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(Article begins on next page)

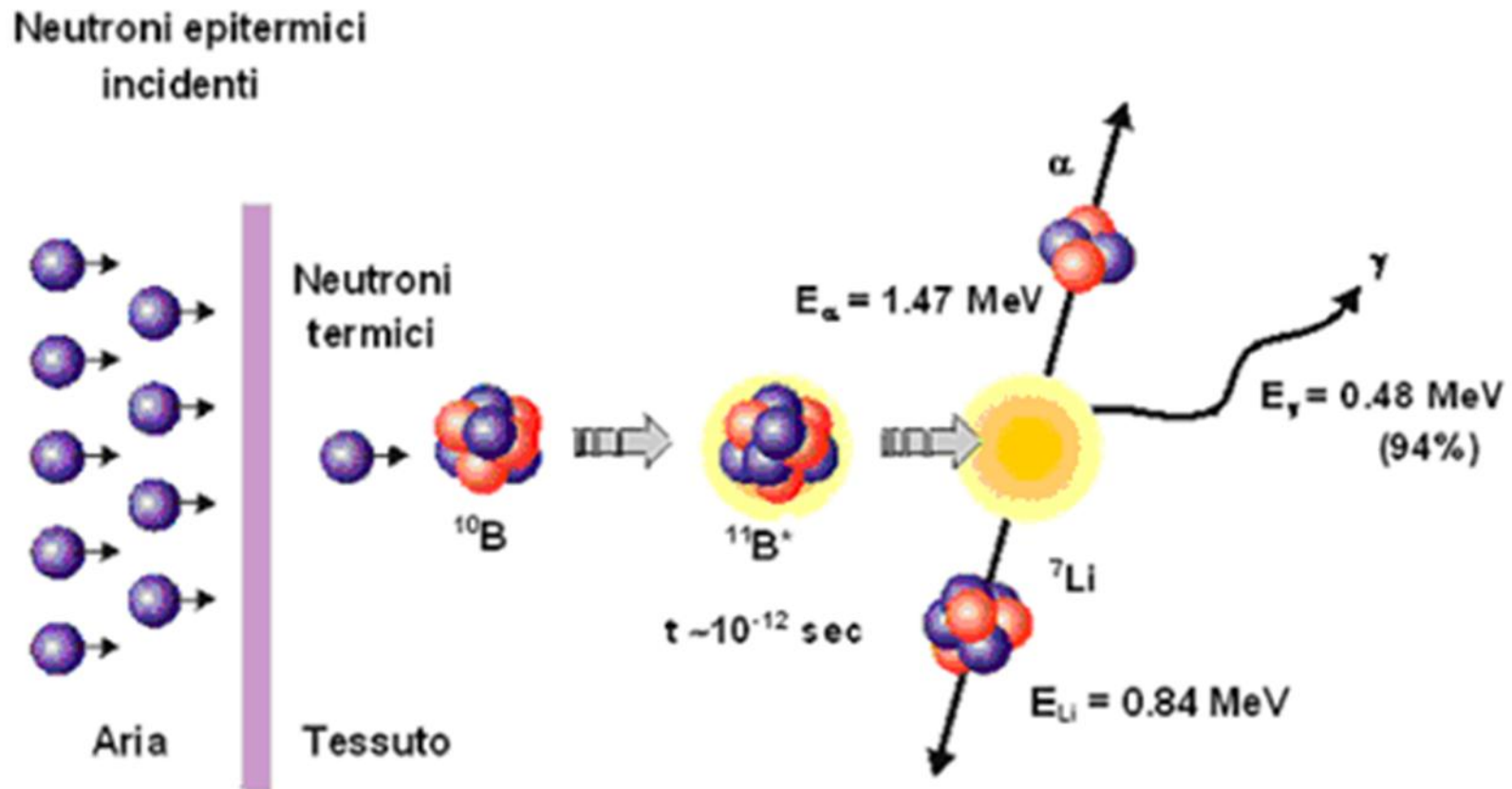
New Synthetic Strategy of MRI/BNCT Agents Based on Hydroboration Reaction

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Boron Neutron Capture Therapy



A. H. Soloway, W. Tjarks, B. A. Barnum, F. G. Rong, R. F. Barth, I. M. Codogni and J. G. Wilson, *Chem. Rev.* **1998**, *98*, 1515.

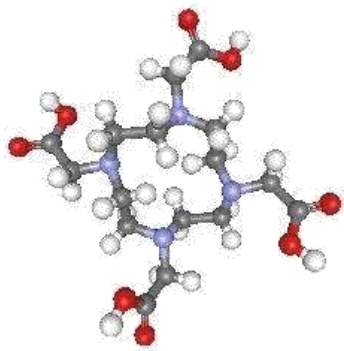
Properties for BNCT agents

- **Low toxicity**
- **Good stability in biological environment**
- **Persistence inside target cells**
- **High boron introduction in tumor tissue:
20 – 35 $\mu\text{g } ^{10}\text{B}$ / 1 gr cancer cells**
- **Concentration ratio cancer tissue/healthy tissue : 3 – 5 / 1**
- **Concentration ratio cancer tissue/blood : 5 / 1**
- **Efficient body scanning**

R. F. Barth, J. A. Coderre, M. G. H. Vicente, T. E. Blue, *Clin.Cancer Res.*, 2005, 11, 3987

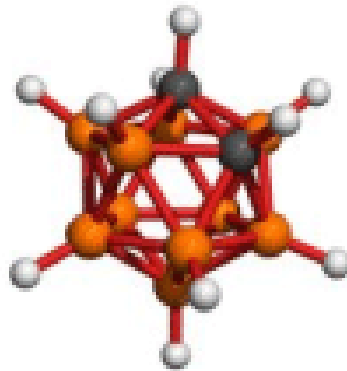
MRI/BNCT dual agent: general structure

MOLECULAR PROBE



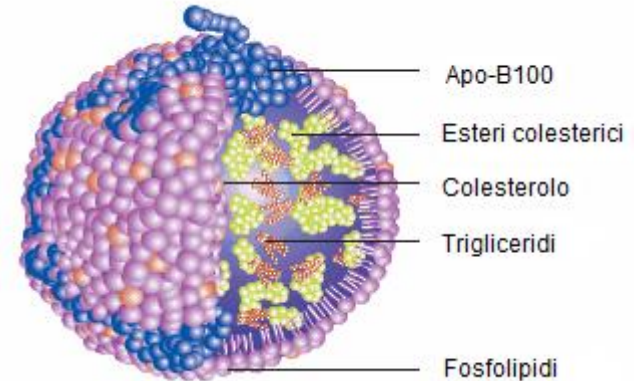
[Gd-DOTA]⁻

CARBORANE



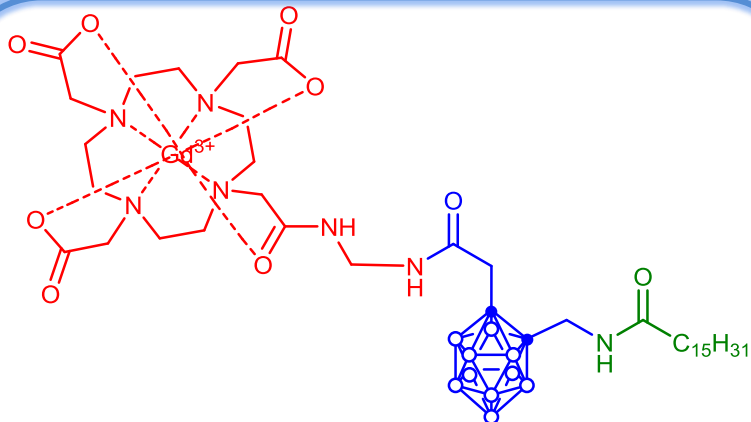
Dicarba-*closo*-dodecaborane

BIOLOGICAL VECTOR

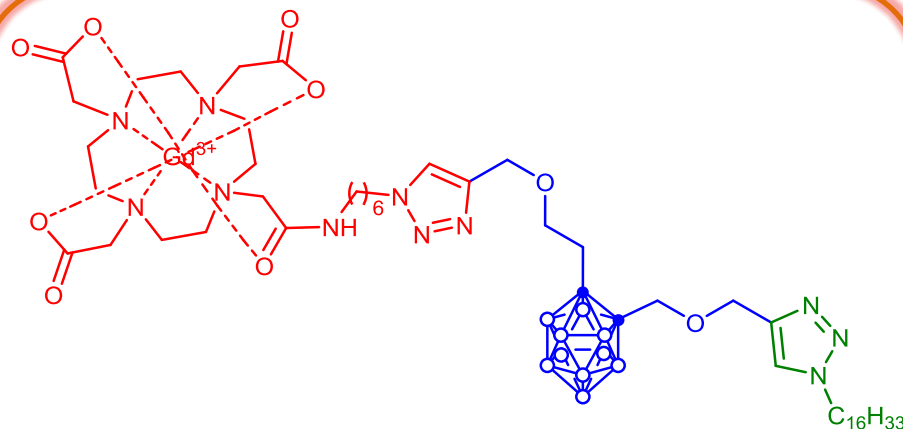


Lipoprotein

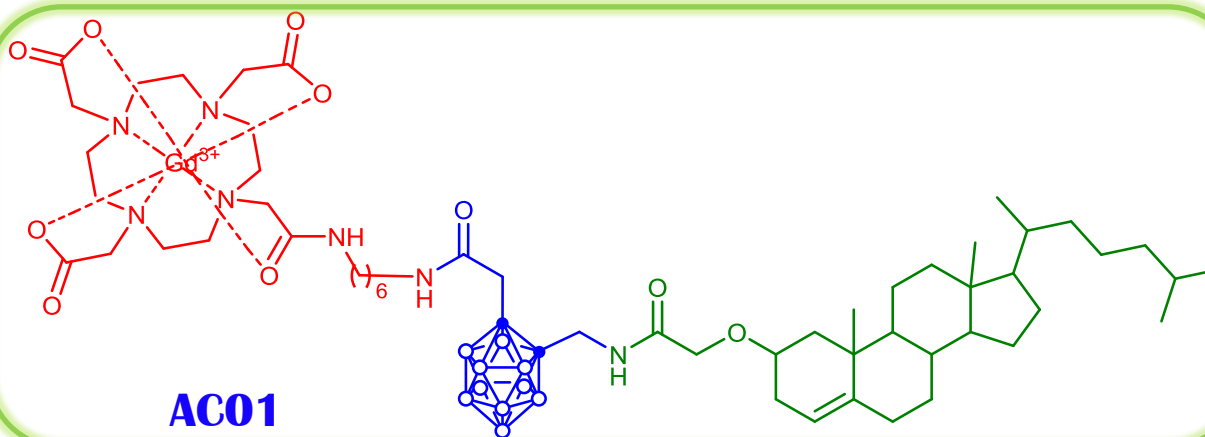
Examples of MRI/BNCT agents



AT101



MEA01



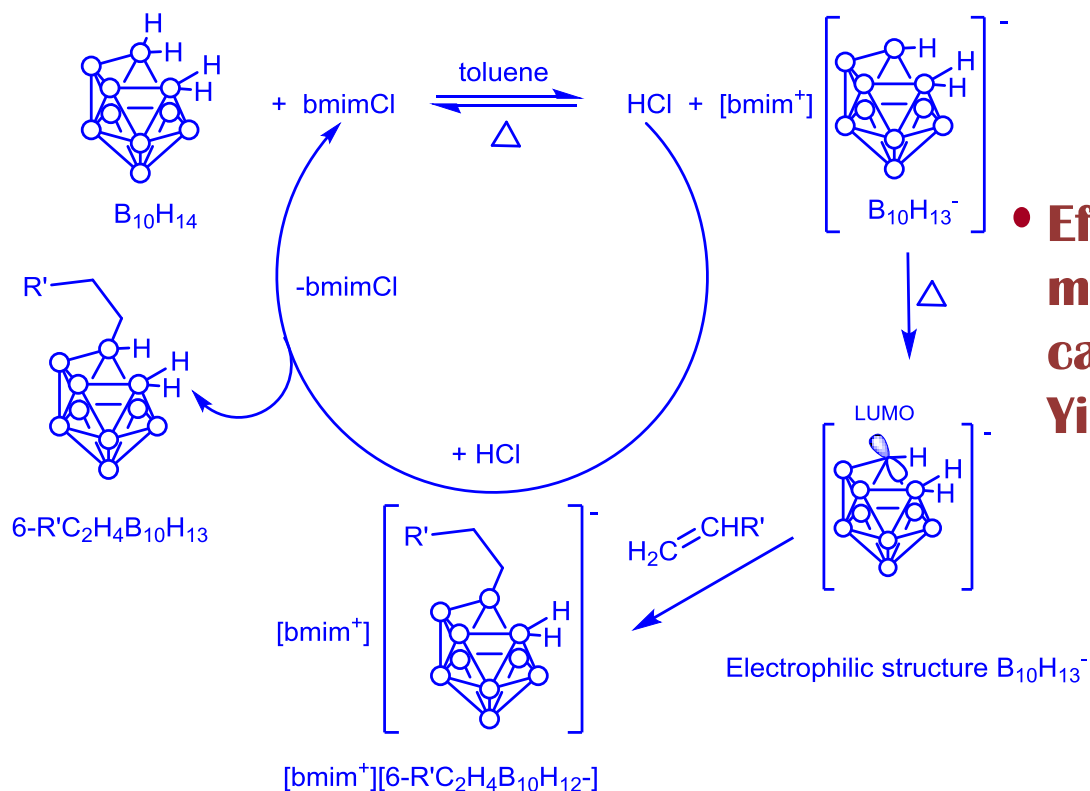
AC01

Org. Biomol. Chem., 2008, 6, 4460

Chem. Eur. J., 2013, 19, 721 – 728

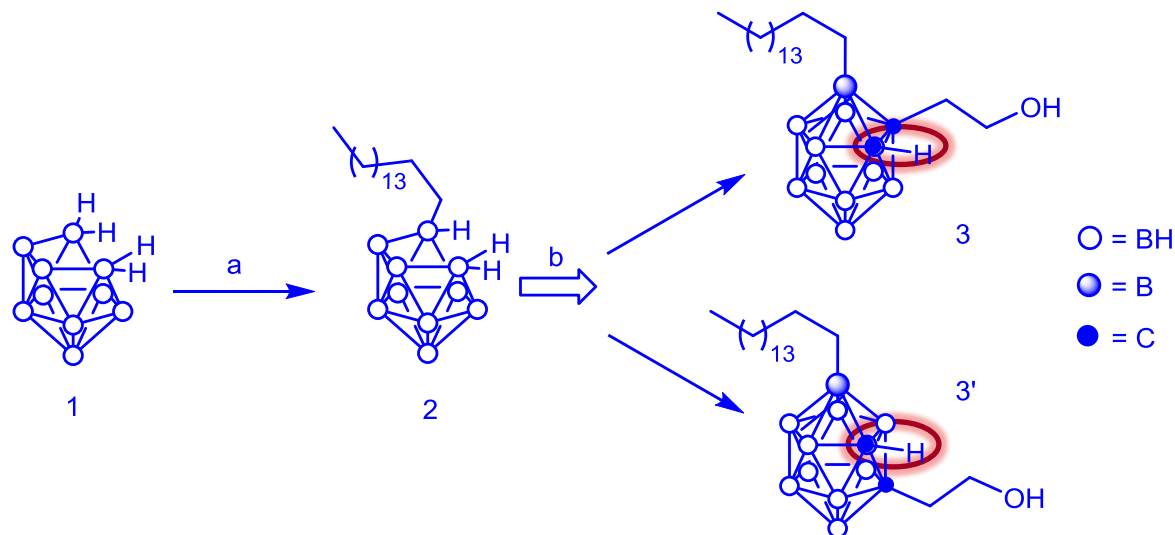
Org. Biomol. Chem., 2014, 12, 2457-2467

New decaborane functionalization strategy: Hydroboration reaction



- **Efficient strategy for lipophilic moiety introduction on boron cage:**
Yield product: 55 – 92 %

New dual agent synthesis: PB01



Synthesis of *C*-(2-hydroxy)-ethyl-*C*-H-6-(hexadecyl)-*o*-carborane (**3**)

a) 1-hexadecene (3.5 eq), bmimCl (0.3 eq), toluene, 125°C, yield 43%; b) 3-butyn-1-ol (4 eq), bmimCl (0.3 eq), toluene, 100°C, yield 40%

Structure 3 : Isomer 1^a

Chemical shift for C-H

¹H: 4.1 ppm

¹³C: 60.35 ppm

Structure 3' : Isomer 2

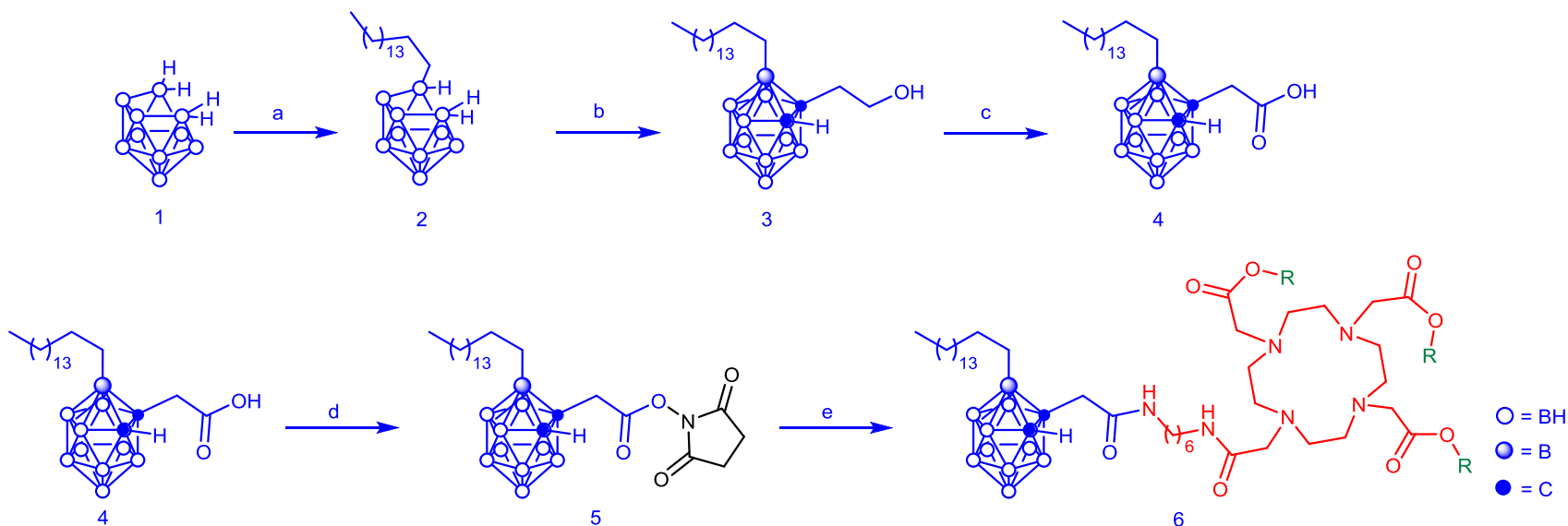
Chemical shift for C-H

¹H: 3.8 ppm

¹³C: 61.47 ppm

^a Molecular structure defined by X-ray diffractometric study
Structure acquired by Dott.ssa Domenica Marabello

New dual agent synthesis: PB01

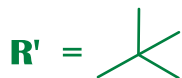


General procedure:

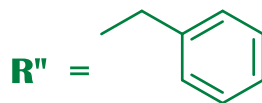
Synthesis of *C*-[R₃-DOTAMA-C₆]-acetamide-*C'*-H-6-(hexadecyl)-*o*-carborane (6)

- a) 1-hexadecene (3.5 eq), bmimCl (0.3 eq), toluene, 125°C, yield 43%; b) 3-butyn-1-ol (4 eq), bmimCl (0.3 eq), toluene, 100°C, yield 40%; c) CrO₃ (4 eq), H₂SO₄ (3M), acetone, room temperature, yield 77%
d) *N*-hydroxysuccinimide [NHS] (1.15 eq), dicyclohexylcarbodiimide [DCC] (1.2 eq), CH₂Cl₂, room temperature;
e) R₃-DOTAMA-C₆ (0.95 eq), diisopropylethylamine [DIEA] (0.95 eq), CH₂Cl₂, room temperature, yield: 13 – 42%

Protecting groups

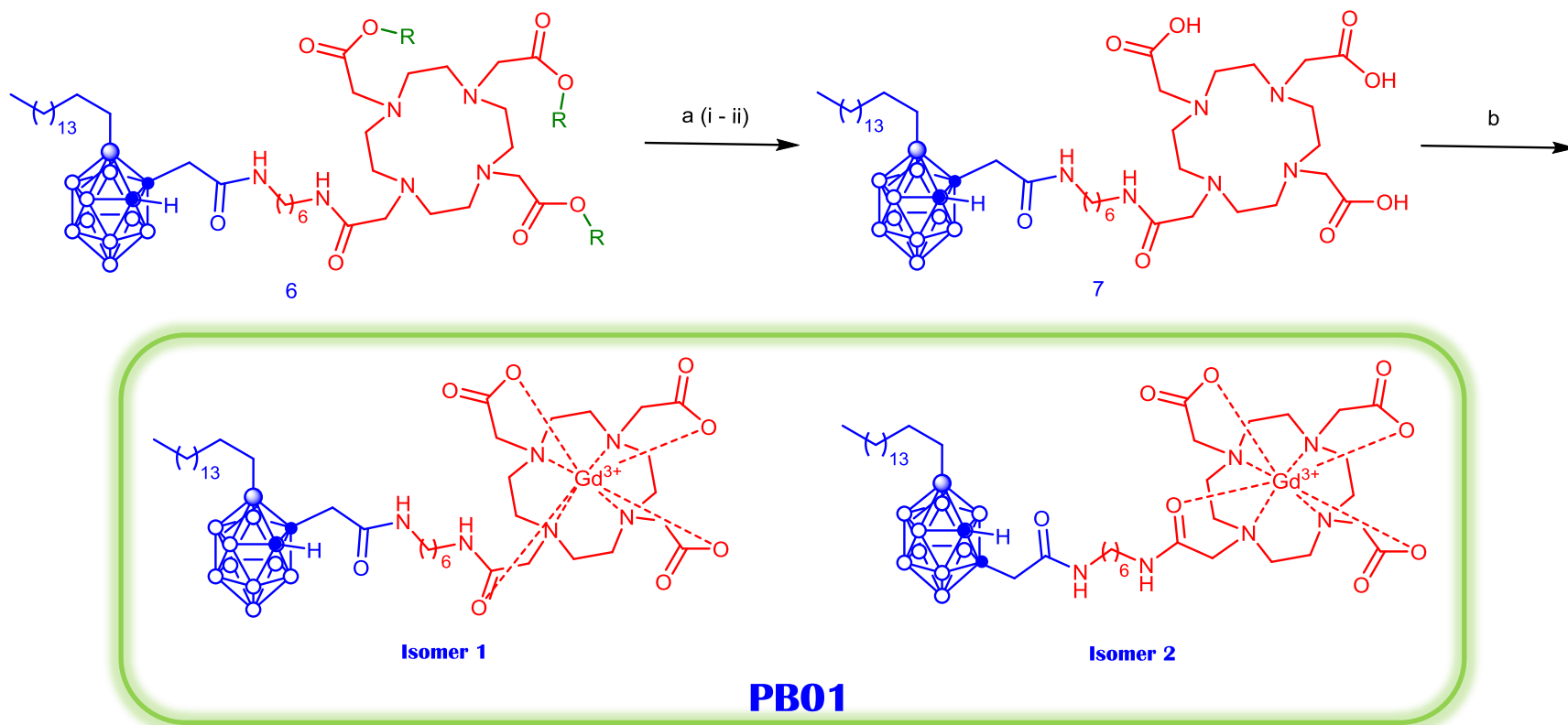


ter-Butyl



Benzyl

New dual agent synthesis: PB01



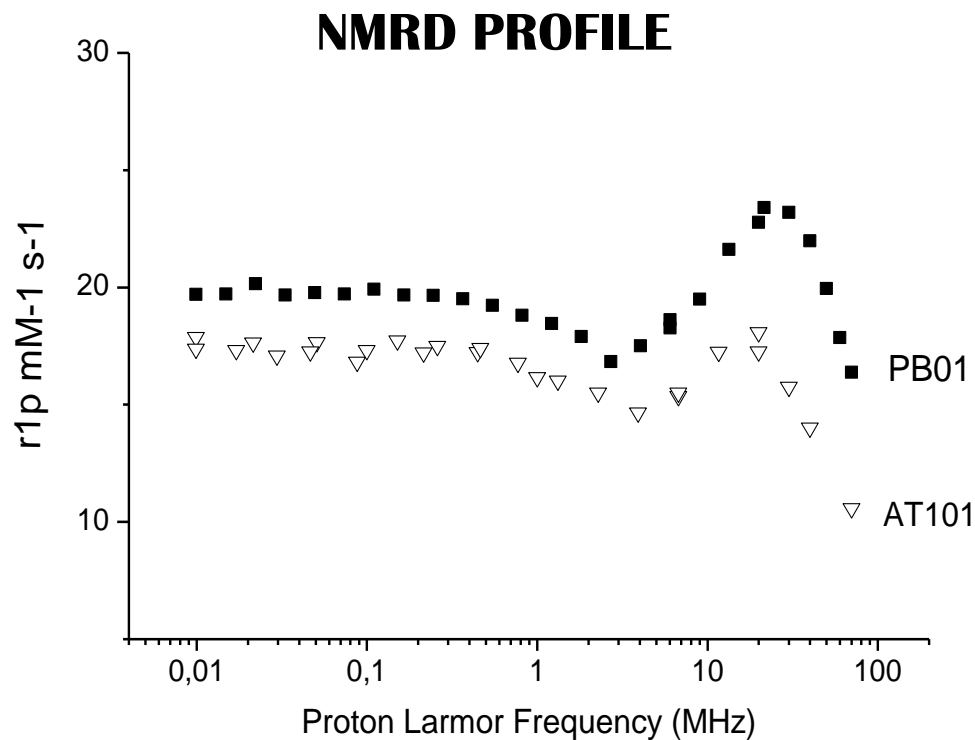
Synthesis of PB01:

a) i R = *ter*-(Butyl) CF_3COOH (2 ml), CH_2Cl_2 , room temperature, yield: > 99%

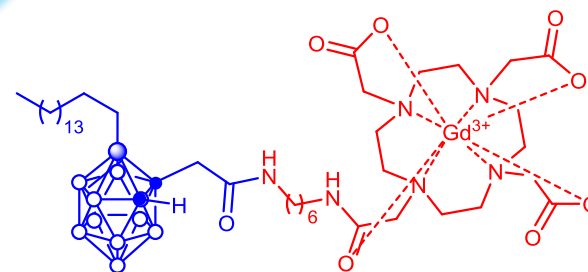
ii R = Benzyl H_2 , Pd on carbon (20% w/w), CH_2Cl_2/CH_3OH (1/1), room temperature, yield: > 99%

b) $GdCl_3$, H_2O , t. amb., pH. 7

Comparison PB01-AT101

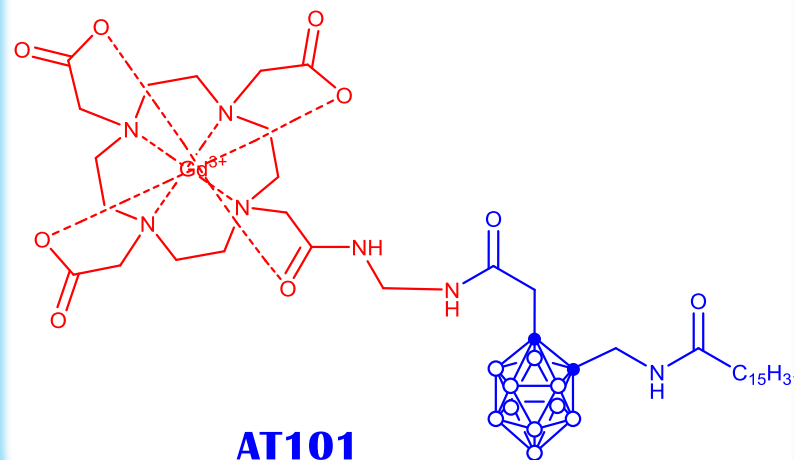


Dott.ssa Simonetta Geninatti Crich
Dott. Diego Alberti



PB01

Synthetic steps required: 6



AT101

Synthetic steps required: 14

Conclusions

Synthesis of MRI/BNCT dual agent based on hydroboration reaction:

- **efficient strategy for lipophilic moiety introduction on boron cage**
- **reduction of synthetic steps required**

Experimental evidence for molecular structure of precursor (3):

X-ray diffractometric study

Preliminary relaxometric tests on PB01 interaction with LDLs show a Nuclear Magnetic Relaxation Dispersion (NMRP) profile superior in comparison with AT101

Aknowledgments

Dott.ssa Domenica Marabello

X-ray diffractometric study

Prof. Claudio Medana

Mass spectra